ERJ Express. Published on February 12, 2009 as doi: 10.1183/09031936.00160208

APNEIC AND OBSTRUCTIVE NON-APNEIC SLEEP RESPIRATORY EVENTS (ONEs)

An easy way to score obstructive sleep apnea

Authors:

Juan F. Masa, MD [1, 7]
Jaime Corral, MD [1,7]
Joaquin Teran, MD [2-7]
Maria J. Martin, MD [1]
Carlos Disdier, MD [1,7]
Manuela Rubio, MD [3,7]
Manuel Mota[3], PRF[4]
José Zamorano, MD[5]
José M. Montserrat[6-7], MD

Centres:

1. Pulmonary Service, San Pedro de Alcántara Hospital, Cáceres, Spain
2. Pulmonary Service, General Yagüe, Burgos. Spain
3. Primary Care Center San Jorge, Cáceres, Spain
4. Mathematics Department, Extremadura University, Badajoz, Spain
5. Rearch unit, San Pedro de Alcántara Hospital, Cáceres, Spain
6. Hospital Clinic. IDIBAPS, Barcelona, Spain
7. CIBER de enfermedades respiratoria (CibeRes), Spain

Requests for reprints:

Juan F. Masa
C/ Rafael Alberti 12, 10005 Cáceres, SPAIN
fmasa@separ.es
Fax: 34 927212696 / Phone number: 34 927230194
Supported by: SEAR, ANCA and FIS ….

ABSTRACT

INTRODUCTION: Obstructive non-apneic event (ONEs) scoring is shrouded in confusion. This is important in mild patients, where precision is crucial.

OBJECTIVES: 1) to identify ONEs using esophageal pressure (EP) (EP-ONEs) and a non-invasive (NI) method (NI-ONEs); 2) to compare both methods of scoring and 3) to determine the contribution of ONE definitions to clinical findings.

METHODS: Patients with suspected sleep apneas (RDI≤10) during a first PSG were subjected to a second with an EP measurement. EP-ONEs and NI-ONEs were defined as an increase in EP or discernible reduction in the amplitude of thoraco-abdominal bands with both desaturation and/or arousal. Bland and Altman's analysis established agreement. Comparisons were made between EP-ONEs, NI-ONEs and clinical findings.

RESULTS: In our sample (n: 90), the addition of an arousal to the NI-ONEs or EP-ONEs with only desaturation increased the number of NI-ONEs by 329% and 362%, respectively. NI-ONEs with arousal and/or desaturation detected 91% of EP-ONEs. The association with sleepiness depended on the incorporation of arousal into the definition of ONEs.

CONCLUSION: In mild patients, the addition of an arousal to ONEs with only desaturation markedly increased RDI, with probable therapeutic implications. Scoring respiratory events as apnea and ONEs is easier and sufficiently accurate.

Word count: 200

KEY WORDS: Sleep apnea syndrome, hypopnea definition, arousal, UARS, RERA.

INTRODUCTION

Although the definition of apnea is universally accepted, there is considerable uncertainty about the definition of hypopnea. Despite the recent guidelines from the American Academy of Sleep Medicine (AASM)[1], its definition is based on consensus rather than on data derived from physiological investigations or outcomes. The AASM guidelines provide two rules for the scoring of hypopnoea: 1) a 30% drop from baseline in the nasal pressure signal excursion (or that of the alternative hypopnea sensor), with a desaturation of 4%; 2) a 50% drop from baseline in the nasal pressure signal excursion (or that of the alternative hypopnea sensor) with a desaturation of 3% or an event associated with an arousal. The respiratory effort-related arousal (RERA) is defined as increased respiratory effort or flattening of the nasal pressure waveform, leading to an arousal when the sequence of breaths does not meet the criteria for hypopnea.

We believe that the aforementioned scoring rules are confused in both physiological and clinical terms. From the physiological point of view, two points should be considered. First, it is difficult to define a quantitative reduction of flow amplitude when using non-quantitative sensors; and secondly, hypopneas and RERA are induced by the same pathophysiological process: upper airway dynamic obstruction. Moreover, a further source of confusion arises from the fact that arousal is a criterion for both the second scoring rule for hypopnea and RERA but it is not considered in the case of the first scoring rule for hypopnea. From the clinical point of view, there are two main considerations: 1) the relationship between respiratory events that do not meet the classical criteria for hypopnea and somnolence. Guilleminault et al[2] highlighted the importance of arousals as a cause of somnolence. A thermistor was used as a sensor and this probably accounts for the failure to recognize events non-invasively[3,4]. Nowadays, other hypopnea sensors[5,6] can identify the amplitude reduction of the flow signal more successfully. 2) The current Medicare guidelines define hypopnea

only in terms of desaturation and do not take into account arousal, as recommended by a) the second scoring rule for hypopnea and b) the scoring rule for RERA. This point is of paramount importance, given that a considerable number of patients with upper airway events and clinical symptoms will not be treated as a result.

Very few papers have addressed this issue to date. Levy´s group[7] was one of the first to analyze the problem of studying patients with moderate sleep apnea. These authors suggested that the distinction between hypopnea and RERA was artificial. They demonstrated that the level of esophageal pressure in hypopnea resembled that of RERA. In the aforementioned study, most of the hypopneas displayed arousal without any desaturation. In severe patients, the effect of major hypopneas will probably cause a marked oxygen desaturation[8-10]. Thus, the addition of an arousal will have less impact in comparison with patients with moderate or mild sleep apnea, where light or subtle hypopneas could be predominant. Given that hypopneas and RERA are dependent on the same mechanism – dynamic obstruction –, and given that the differences between them could be attributed to the type of flow sensors used, it seems reasonable to score them jointly.

We hypothesize that dividing the respiratory events into apneas (static obstruction) and ONEs (dynamic obstruction) is more representative of the physiopathology of upper airway occlusion and provides the same information as that obtained by taking into account all the different types of non-apneic events. Furthermore, in the clinical arena, non-quantitative sensors are routinely used, even though quantitative data are being measured; this discrepancy can lead to errors. Furthermore, the task of subdividing ONES into so many groups is ultimately time-wasting. To test this hypothesis, our aims were as follows: 1) to identify ONEs using esophageal pressure (EP) – (EP-ONEs) – or non-invasive method (NI) – (NI-ONEs); 2) to compare the scoring with the EP-ONEs vs NI-ONEs definitions, and 3) to evaluate the different ONE definitions with respect to clinical findings.

METHODS

Study population

We prospectively analyzed a cohort of 90 patients with suspected sleep apnea syndrome (SAHS) in whom an initial full polysomnography showed an apnea and hypopnea index ≤10. Apneas were defined as an absence of nose-mouth thermistor flow ≥10 seconds. Hypopnea was defined as a discernible reduction in thermistor airflow for at least 10 seconds with ≥3% oxygen desaturation or final arousal[11]. Owing to the presence of symptoms, another full polysomnography was performed with esophageal pressure measurement.

Protocol and measurements

All subjects were asked to complete the same questionnaire about symptoms of SAHS and other diseases causing sleepiness, and to provide a subjective measurement of sleepiness (Epworth Sleepiness Scale)[12]. The two polysomnographies recorded the electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, oxyhemoglobin saturation, oral-nasal airflow by thermistor and thoracoabdominal movements by automatically calibrated inductance plethysmography (Respitrace; NIMS, Miami Beach, Florida). Sleep data were scored in accordance with the criteria of Rechtschaffen and Kales[13]. An arousal was defined according to the criteria of the AASM[1]. In the second polysomnography, an additional transnasal esophageal catheter was introduced and calibrated, following the previously described technique[14] .The protocol study was approved by the Institutional Research Committee and written consent was obtained from the patients.

As mentioned, the major aim of this paper was to correlate the different variables obtained from the second polysomnography. The role of the first polysomnography was to select

patients with probable mild SAHS because a number of patients could have an AHI >10 for technical reasons (underestimation of hypopneas by thermistor).

Scoring and definitions in the second polysomnography

Three different scoring rounds were undertaken. In the first, the esophageal pressure signal was hidden from the computer screen and the neurological and respiratory variables were assessed, using the same criteria as in the first polysomnography. In the second round, ONEs were scored on the basis of thoracoabdominal bands (NI-ONEs) hiding the esophageal pressure measurement, and in the third round the score was based on esophageal pressure (EP-ONEs). We then calculated the different indexes, as shown in Table 1, according to different definitions of ONEs, as well as their subclasses, based on 1) the EP pressure measurement associated with an arousal and/or a desaturation and 2) a reduction in the thoracoabdominal motion associated with an arousal and/or a desaturation. Concurrent events (NI-ONEs and EP-ONEs) were not recorded**.**

Intra- and inter-observer agreement

To evaluate the intra-observer agreement, the technician responsible for the scoring reanalyzed the polysomnographies blindly in eight subjects (chosen at random), using the same criteria as in the second and third scoring rounds to identify NI-ONES or EP-ONEs (desaturation/arousal) and NI-ONES or EP-ONEs (desaturation). Moreover, to evaluate the inter-observer agreement, another technician with similar experience from the same sleep laboratory analyzed the same eight subjects twice, using the same protocol. Finally, a researcher (JFM) examined the agreement by reviewing the same polysomnographic recording. A total of 3,892 epochs of sleep time with esophageal pressure measurement were checked in each agreement.

Number of RERAs

The difference between EP-ONEs (arousal) and NI-ONEs (arousal) was considered as the true RERA.

Statistical analysis:

Proportions of patients with sleep apnea were evaluated at three different EP-RDI and NI-RDI cut-off points (≥5, ≥10 and ≥15), in the light of the diverse definitions of ONEs.

To determine the association between NI-RDI and the Epworth sleepiness scale, we compared the mean of NI-RDI (desaturation) and the mean of NI-RDI (desaturation/arousal) in accordance with terciles of the Epworth sleepiness scale. We initially used one-way ANOVA. Where appropriate, differences between individual means were tested using the LSD (least significant difference) (SPSS 14.0, SPSS inc, Chicago). If the variables were not distributed normally, a non-parametric test was used (Kruskal Wallis and Dunn post hoc to identify differences between individual means).

A Bland and Altman analysis was carried out[15] to verify the agreement of the EP-ONE and NI-ONE indexes and to ascertain whether the differences were independent of the measurement size. The analysis was performed with the differences in the EP-ONE (desaturation) and NI-ONE (desaturation) indexes and the mean of the EP-ONE (desaturation) and NI-ONE (desaturation) indexes. Other analyses were carried out on the differences in the EP-ONE (desaturation/arousal) and NI-ONE (desaturation/arousal) indexes and the mean of the EP-ONE (desaturation/arousal) and NI-ONE (desaturation/arousal) indexes.

An event-by-event analysis was performed with the Kappa test[16,17] to determine the intra-observer and inter-observer agreement, excluding the random effects classifying NI-ONEs and EP-ONEs.

RESULTS

Table 2 shows the anthropometric, clinical and polysomnographic variables of the sample. Patients constituted a middle-aged, mainly male and slightly overweight population with some clinical and polysomnographic characteristics habitually observed in patients with sleep apnea.

Table 2 also shows the respiratory events expressed as the apnea plus ONE index (EP-RDI and NI-RDI), using the different definitions of ONEs. As observed, the EP-RDI (desaturation) and NI-RDI (desaturation) show a three-to-fourfold increase when arousal was added to the definition.

Figure 1 shows the data with regard to the number of apneas, NI-ONEs and EP-ONEs. The total number of respiratory events identified in the 90 patients studied was: 311 apneas, 877 NI-ONEs (desaturation), 898 EP-ONEs (desaturation), 2,890 NI-ONEs (arousals) and 3,250 EP-ONEs (arousals). The sum of the NI-ONEs (desaturation) plus those with arousal, NI-ONEs (desaturation/arousal), was 3,767, whereas the sum of EP-ONEs (desaturation) plus those with arousal, EP-ONEs (desaturation/ arousal), was 4,148. In summary, if we add the arousal to NI-ONEs (desaturation) and EP-ONEs (desaturation), the number of NI-ONEs increases by 329% and by 362%, respectively. Therefore, the number of true RERAs would be the difference between 3,250 EP-ONEs (arousals) and 2,890 NI-ONEs (arousals). That means that 9% of the classic RERAs are not detected by our definition of NI-ONEs.

Figure 2 shows the prevalence of sleep apnea by means of three cut-off points of RDI. The prevalence using EP-RDI or NI-RDI (desaturation/arousal) was 2 to 11 times higher than that observed when only EP-RDI or NI-RDI (desaturation) was used.

Figure 3 shows that there was no increase in NI-RDI (desaturation) according to the Epworth sleepiness scale terciles. However, the association was significant ($p<0.001$) when arousal was included in the definition of ONE, with NI-RDI (desaturation/arousal). Furthermore the Epworth sleepiness scale was significantly correlated with the arousal index ($R=0.373$; $P<0.001$). This could lead to an increase in the number of patients in need of treatment.

Figure 4 shows the Bland and Altman analysis between: EP-ONE index (desaturation) and NI-ONE index (desaturation) (top); EP-ONE index (desaturation/arousal) and NI-ONE index (desaturation/arousal) (bottom). The difference between the EP-ONE-index (desaturation) and the NI-ONE-index (desaturation) was 0.4±1. The difference between EP-ONE-index (desaturation/arousal) and the NI-ONE-index (desaturation/arousal) was 1.9±2.8. The difference between the EP-ONE-index and NI-ONE-index was independent of the measurement size.

Finally, the intra- and inter-observer agreement: the intra-observer agreement (Kappa test) was 0.82 for NP-ONEs (desaturation/arousal) and 0.93 for EP-ONEs (desaturation/arousal). The inter-observer agreement was 0.86 for NI-ONEs (desaturation/arousal) and 0.90 for EP-ONEs (desaturation/arousal). The intra-observer agreement was 0.87 for NP-ONEs (desaturation) and 0.96 for EP-ONEs (desaturation). The inter-observer agreement was 0.90 for NI-ONEs (desaturation) and 0.94 for EP-ONEs (desaturation).

DISCUSSION

This study reviews a large numbers of ONEs and shows that, in our selected population, arousal plays the major role in RDIs, especially in more symptomatic patients. Furthermore, the use of esophageal pressure instead of bands (our definition) for the ONE classification only increases the number of RDIs by 9%. In the highest Epworth Sleepiness Scale tercile

(13.8±3.2), the NI-RDI changed from 3.6±4.9 with only desaturation to 18.8±14.9 with desaturation and/or arousal. This finding could have therapeutic implications.

The ONE definition proposed – discernible reduction in the band amplitude with arousal and/or fall in SaO2 – is more suitable than those proposed by the AASM, given that: 1) the majority of the sensors used in clinical practice are non-quantitative (AASM definitions quantify the degree of flow reduction) and 2) most ONEs are associated with arousal alone (77%) (the first AASM hypopnea definition does not include arousal). It is therefore reasonable to assume that the recommended AASM hypopnea definition does not embrace many obstructive events.

Cracowski et al[7] carried out a study with a similar objective and with similar criteria for patient selection. Moreover, they found that 63% of their 1,061 EP-ONEs had cortical arousal with no oxygen desaturation. Other authors, however, have not obtained similar results[8-10]. These discrepancies could be attributed to varying definitions of hypopnea or differences in the sensors or criteria for patient selection. In our study, as in Cracowski's, the subjects were selected on the basis of suspected moderate-mild sleep apnea and a limited number of oxygen desaturations. In contrast to typical sleep apnea patients[8-10], Cracowski's study – and our study herein – showed a low body mass index[8,9]. A higher BMI or greater breathing reduction could induce more oxygen desaturation, thereby reducing the contribution of arousal to hypopnea detection.

The standard AASM hypopnea definition does not include arousal, largely because of a study that demonstrated the greater reliability of desaturation[18]. The intra-class correlation coefficient (ICC) was 0.97 considering RDI with desaturation ≥3% alone, 0.77 considering only arousal and 0.95 considering desaturation ≥3% or arousal. Our more powerful event-by-event analysis (Kappa test) reveals the same phenomenon, but with a lower magnitude. As

indicated above, our explanation is that desaturation habitually coincides with a greater reduction in breathing, in which case it is easy to recognize; ONEs with arousal alone coincide more frequently with a lower reduction in breathing and are more difficult to identify. Anyway, the reliability level for desaturation/arousal was very good, which means that this method can be applied in clinical practice.

Although esophageal pressure is the standard for measuring respiratory effort[19], it is not able to distinguish between hypopneas and RERAs. When considering our definition of NI-ONE as discernible reductions in thoracic-abdominal bands plus desaturation and/or arousal, only 9% of the EP-ONEs were undetected. Accordingly, we regarded this group as true RERAs. Similar results were found in Cracowski's study, where the RERAs accounted for only 5% of the total ONEs when the flow is measured by pneumotacography and the effort by esophageal pressure. Thus, the number of ONEs identified in the present study resembles the level achieved in the current practice of polysomnography, where slight reductions in the flow measurement are taken into account. Given that RERAs and hypopneas have the same physiopathological etiology and even similar clinical symptoms, it may be assumed that the definitions of these events overlap. The scoring of the two events should therefore be performed jointly in order to simplify routine practice.

The sleep apnea prevalence increased 2 to 11 times more when arousal was considered in the ONE definition (Figure 2). Differences in prevalence between non-invasive and invasive methods (NI-RDI and EP-RDI) were small and were mainly found when desaturation/arousal criteria were applied. These differences were higher in the lower cut-off points of diagnosis. We believe that this is probably explained by the detection of RERA events by the invasive method.

One limitation of the present study is that we did not use nasal pressure as the flow sensor to score the number of hypopneas and RERAs. Instead, we used thoracoabdominal bands (inductance plethismography), regarded as an alternative hypopnea measurement[1,20]. Bands calibrated with a known volume have been considered appropriate for obtaining breath volume[21] with a good agreement with nasal pressure[22,23]. We did not calibrate the inductance plethismography device with a known volume but instead used auto-calibration. We found that inductive plethismography satisfactorily identifies ONEs when compared with the standard respiratory effort measurement (esophageal pressure). Accordingly, similar results would be expected when using nasal pressure. However, it could be possible that the amount of RERAs detected would be slightly higher with nasal prongs measurements, reducing our 9% of undetected RERAs.

Thus, arousal plays a major role in the detection of respiratory events in mild sleep apnea patients, and this could have therapeutic implications. Arousal should therefore always be added to the recommended AASM hypopnea definition, in order to enhance the evaluation of this population. If scoring were based on a discernible reduction in the amplitude of the breathing signal with arousal and/or desaturation, almost all respiratory events (hyponeas and RERAs) would be detected. We suggest that non-apneic respiratory events should therefore be scored jointly in order to simplify routine practice.

ACKNOWLEDGEMENTS:

We are indebted to Verónica Rodríguez and Vanessa Iglesias for assistance in the translation of the manuscript and Asunción Martín and Carmen Lorenzana for technical assistance.

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LEGENDS OF FIGURES

Figure 1: Number of respiratory events. Most of the events were EP-ONEs or NI-ONEs with arousal (without oxygen desaturation). Abbreviations: EP-ONEs: obstructive non-apneic events measured by using the esophageal pressure (EP); NI-ONEs: obstructive non-apneic events measured by using bands (NI).

Figure 2: Prevalence of sleep apnea at three cut-off points. The prevalence using EP-RDI or NI-RDI (desaturation/arousal) was 2 to 11 times higher that observed when EP-RDI or NI-RDI (desaturation) were used. Minor differences were observed between EP-RDI (desaturation/arousal) and NI-RDI (desaturation/arousal). Abbreviations: EP-RDI: apneas plus obstructive non-apneic events index measuring the ONEs by using the esophageal pressure (EP); NI-RDI: apneas plus obstructive non-apneic events index measuring the ONEs by using bands (NI).

Figure 3: Non-invasive respiratory disturbance index (NI-RDI) distribution in accordance with Epworth sleepiness scale (EES) terciles. In NI-RDI (desaturation/arousal), all the individual comparisons were statistically significant. In NI-RDI (desaturation), only the lowest versus intermediate terciles were statistically significant. (*= lowest versus intermediate terciles for NI-RDI (desaturation) was $p<0.05$ and for NI-RDI (desaturation/arousal) $p<0.001$. †= intermediate versus highest terciles for NI-RDI (desaturation/arousal) was $p<0.05$. ‡= lowest versus highest terciles for NI-RDI (desaturation/arousal) was $p<0.001$).

Figure 4: Bland and Altman analysis between: EP-ONE index (desaturation) and NI-ONE index (desaturation) (top); EP-ONE index (desaturation/arousal) and NI-ONE index (desaturation/arousal) (bottom). Minor differences were found in both the analyses, regardless of the measurement size. Abbreviations: EP-ONE index: obstructive non-apneic events index measuring the ONEs by using the esophageal pressure (EP); NI-ONE index: obstructive non-apneic events index measuring the ONEs by using bands (NI).

TABLE 1. Definition of obstructive non-apneic events (ONEs) based on the type of sensor and their consequences. Definition of the number of events per hour (RDI) corresponding to the number of apneas and ONEs per hour and similarly based on the type of sensor used and their consequences.

Esophageal Pressure (EP-ONES)

1. EP-ONEs (desaturation): a progressive increase in esophageal pressure for at least 10 seconds, followed by a ≥3% oxygen desaturation;
2. EP-ONEs (arousal): a progressive increase in esophageal pressure for at least 10 seconds, followed by an arousal;
3. EP-ONEs (desaturation/arousal): a progressive increase in esophageal pressure for at least 10 seconds, followed by a ≥3% oxygen desaturation and/or arousal.

Thoraco-Abdominal Bands (Non-invasive breathing measurement) NI-ONEs

1. NI-ONEs (desaturation): a discernible decrease in the thoraco-abdominal motion for at least 10 seconds, followed by a ≥3% oxygen desaturation:
2. NI-ONEs (arousal): a discernible decrease in the thoraco-abdominal motion for at least 10 seconds, followed by an arousal;
3. NI-ONEs (desaturation/arousal): a discernible decrease in the thoraco-abdominal motion at least 10 seconds, followed by a ≥3% oxygen desaturation and/or arousal.

APNEA + ONEs Index (Events per hour): RDI (Respiratory Disturbance Index)

1. EP-RDI (desaturation): nº of apneas + EP-ONEs (desaturation)
2. EP-RDI (arousal): nº of apneas + EP-ONE (arousal)

3. NI-RDI (desaturation): nº of apneas + NI-ONEs (desaturation)
4. NI-RDI (arousal): nº of apneas + NI-ONEs (arousal)

5. NI-RDI ((desaturation/arousal): nº of apneas + NI-ONEs (desaturation/ arousal)
6. NI-RDI (desaturation/arousal): nº of apneas + NI-ONEs (desaturation/arousal)

TABLE 2: Anthropometric, clinical and polysomnographic variables (second polysomnography) from the total sample.

	N= 90
Age, yr	44±10
Sex, male%	81
Body mass index (Kg/m^2)	28±4
Habitual snorer, %	89
Apneas observed, %	54
Morning fatigue, %	61
Nocturia, %	32
Epworth Sleepiness Scale	9±4
Hypertension, %	27
Shift work, %	13
TST, min*	262±62
Sleep time lost, min†	28±60
Light sleep, %	38±10
Deep sleep, %	21±10
REM sleep, %	10±6
Arousal index	29±16
Sat O2 below 90%, % of TST	6±17
AHI (thermistor)	3.9±5.4
EP-RDI (desaturation)	3.6±4.7
NI-RDI (desaturation)	3.3±4.3
NI-RDI (desaturation/arousal)	11±11
EP-RDI (desaturation/arousal)	13±13

Abbreviations: TST: total sleep time; AHI: apnea and hypopnea index measured by the thermistor. EP-RDI= apneas plus obstructive non-apneic events measured by using the esophageal pressure (EP); NP-RDI= apneas plus obstructive non-apneic events measured by using bands (NI) * TST with esophageal pressure measurement functioning normally. † Sleep time lost caused by poor signal from the esophageal pressure catheter.

Figure 1

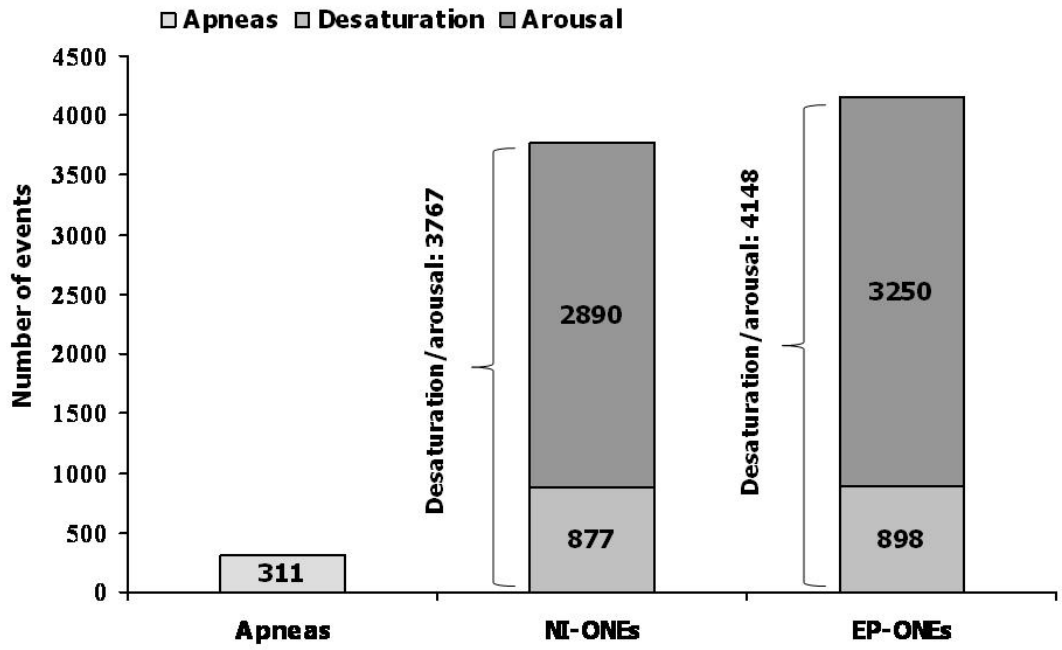
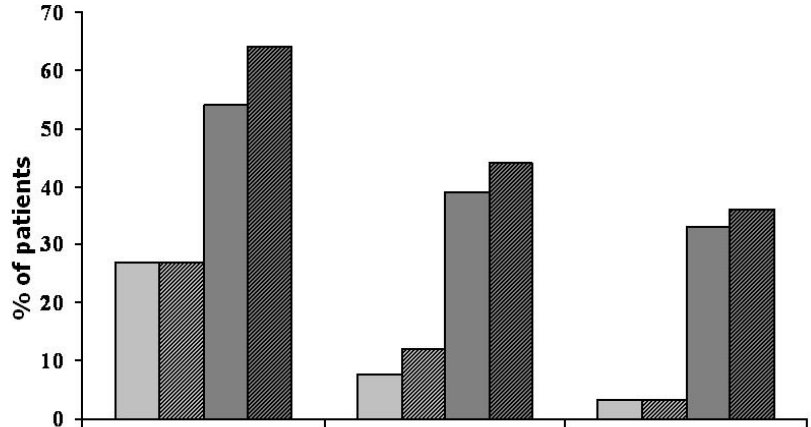

Apneas
Desaturation
Arousal
Number of events
4500
4000
3500
3000
2500
2000
1500
1000
500
0
311
Desaturation/arousal: 3767
2890
877
Desaturation/arousal: 4148
3250
898
Apneas
NI-ONEs
EP-ONEs

Figure 2:



	≥5	>10	≥15
NI-RDI (desaturation), %	27	7,8	3,3
EP-RDI (desaturation), %	27	12	3,3
NI-RDI (desaturation/aorusal), %	54	39	33
EP-RDI (desaturation/arousal), %	64	44	36

Sleep apnea prevalence

Figure 3:

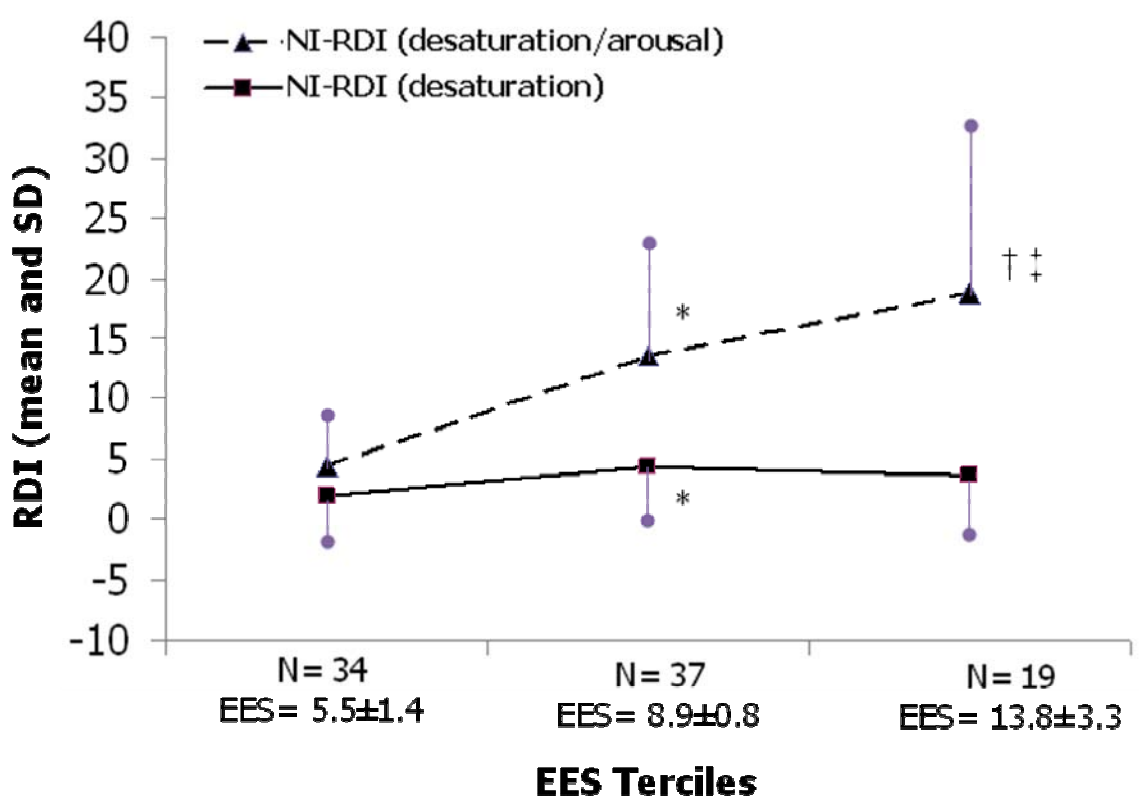
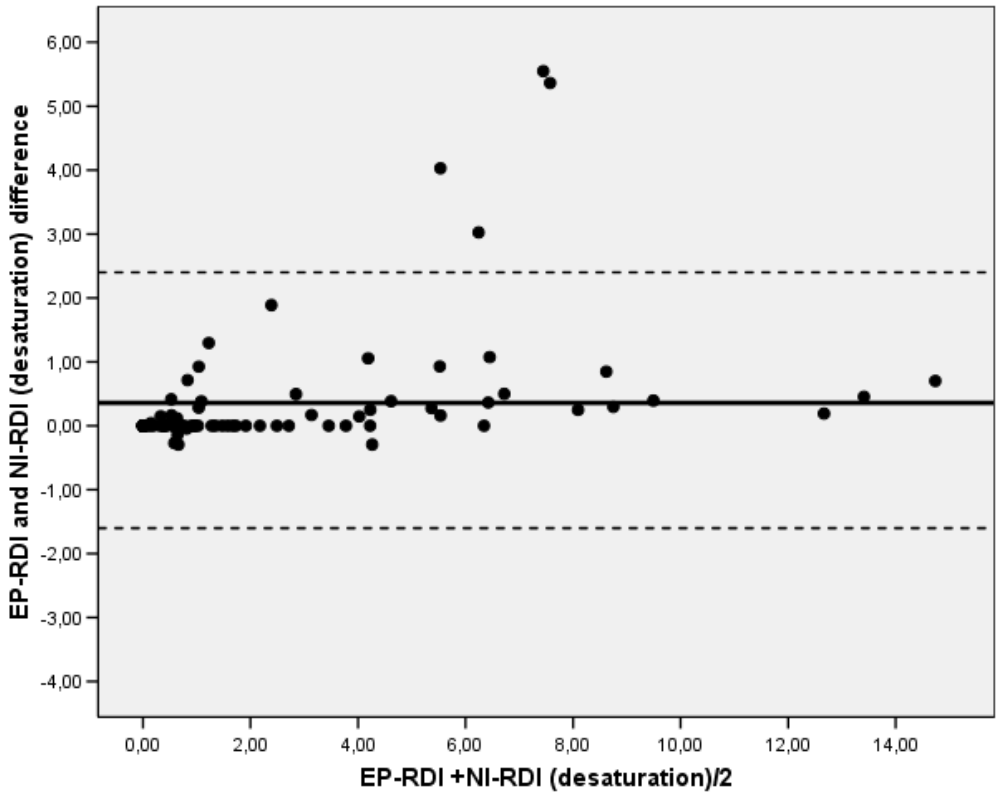
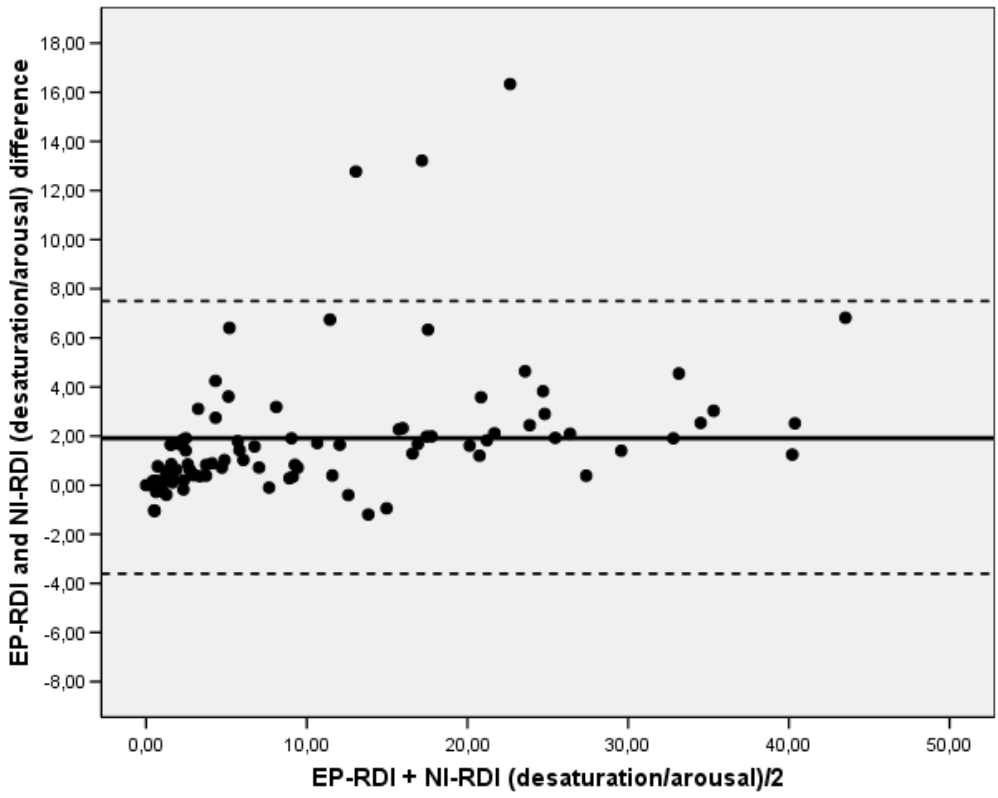

NI-RDI (desaturation/arousal)
NI-RDI (desaturation)
RDI (mean and SD)
40
35
30
25
20
15
10
5
0
-5
-10
*
*
† ‡
N= 34
EES= 5.5±1.4
N= 37
EES= 8.9±0.8
N= 19
EES= 13.8±3.3
EES Terciles

Figure 4


6,00
5,00
4,00
3,00
2,00
1,00
0,00
-1,00
-2,00
-3,00
-4,00
EP-RDI and NI-RDI (desaturation) difference
0,00
2,00
4,00
6,00
8,00
10,00
12,00
14,00
EP-RDI +NI-RDI (desaturation)/2


18,00
16,00
14,00
12,00
10,00
8,00
6,00
4,00
2,00
0,00
-2,00
-4,00
-6,00
-8,00
EP-RDI and NI-RDI (desaturation/arousal) difference
0,00
10,00
20,00
30,00
40,00
50,00
EP-RDI + NI-RDI (desaturation/arousal)/2